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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,390	02/12/2001	Samuel T. Labrie	PF-0232-1 DIV	8952

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INCYTE GENOMICS, INC.
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EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	7

DATE MAILED: 09/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 7/2/02

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-21 is/are pending in the application.
Of the above, claim(s) 3-15, 18-21 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1, 2, 16, 17 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-21 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election with traverse of Invention I, claims 1, 2, 16 and 17 in Paper No. 6, filed 7/2/02, is acknowledged. The traversal is on the ground(s) that (1) methods of using the elected protein should be rejoined in light of *in re Ochiai*, and (2) the examination of the entire application, in particular antibodies with the protein would not constitute a burden to search. This is not found persuasive because with respect to point (1), Applicants argument of the decisions in *In re Ochiai* and *In re Brouwer* is noted but is not deemed persuasive, as PTO practice in view of those decisions is directed to rejoinder of claims after allowable subject matter has been indicated, and not to withdrawal of restriction requirements. Applicants are advised that at such time as the elected product claim(s) are indicated as being allowable, rejoinder of claims drawn to methods of using such may be requested under 35 U.S.C. §103(b) pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86). Such rejoinder is *not* tantamount to a withdrawal of the restriction requirement. With respect to point (2) above, contrary to applicants' assertion that any search of the prior art in regard to group I will reveal whether any prior art exists as to the other Groups, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. For example, there are many antibodies described in the art for whom the protein to which they bind was not known at the time of discovery of the antibody. A search for an antibody requires a divergent search from that required for the protein to which it binds.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 2, 16 and 17 are under consideration.

Objections and Rejections under 35 U.S.C. §§101 and 112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 16 and 17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The claims are drawn to a protein designated NHT, fragments and derivatives thereof, including the protein of SEQ ID NO: 1, as well as compositions comprising the aforementioned. The protein was isolated on the basis of its homology to TUBBY proteins, and has about 49% identity to human and mouse TUBBY, a.k.a. "TUB". The specification asserts that the protein is expressed in four brain and one lymph node cDNA library (based upon nucleic acid expression), and that it therefore "appears to be associated with mammalian appetite and eating disorders" (page 22, line 27). The specification further asserts that polynucleotides encoding the protein may be used for diagnosis or treatment of a number of diseases (see page 33, first paragraph), as can antibodies to the protein. There appears to be no specific asserted utility for the claimed protein itself, although there is an implicit assertion that the protein can be used to make antibodies to be used for diagnosis/treatment of the diseases listed at page 33.

The assertion that the disclosed NHT has biological activities similar to known TUBBY cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF

and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). Further, other TUBBY-related proteins have been found to be associated not with appetite or eating disorders, but with ocular diseases: North et al., PNAS 94:3128 report that TULP1 and TULP2, which are 'tubby-like proteins' with 60-90% identity to TUBBY in their N-terminal portions, are likely to be associated not with appetite, but with ocular diseases. Gu et al., Lancet 351:1103 confirm that TULP1 mutations were found in 171 patients with retinitis pigmentosa. In this case, NHT has only 49% homology to the related TUBBY; clearly function cannot be credibly extrapolated from one to the other.

With respect to diagnostic and treatment utilities, although the specification provides a list of diseases, there is no credible link between the disclosed NHT and any of the mentioned diseases. Even if a credible link were established for the disclosed nucleic acids, such would not be sufficient to confer utility to the protein, as it is not recognized in the art that nucleic acid levels are predictive of protein levels. For example, see Haynes et al. (Electrophoresis 19:1862-1871, 1998), studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Haynes concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (page 1863, 2nd paragraph, and Figure 1). Therefore, there is no specific, substantial and credible utility disclosed for the claimed protein and compositions, nor for antibodies that might be made using the claimed protein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 16 and 17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, even if it were found that the specification were enabling for a protein of SEQ ID NO: 1, enablement would not be commensurate in scope with claims to proteins which comprise biologically of immunogenically active fragments thereof, nor for naturally occurring proteins with 90% sequence identity to such:

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification does not disclose any biological activity for NHT. It is not predictable what such activity is, nor is there guidance or working examples of such. Accordingly, it would take undue experimentation to discover biological activities of NHT and then determine what fragments or variants might conserve such. Further, either the biologically or immunogenically active fragments may be embedded within other proteins, which might be naturally occurring; the specification provides no guidance as to the properties or uses of such proteins.

With respect to naturally occurring variants with 90% sequence identity, function of such variants is not predictable (see rejection under 35 U.S.C. § 101, above), and the specification provides no guidance, direction, nor working examples of such. Accordingly, such variants are not enabled.

Claims 1 and 16 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 16 are directed to polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 1 or naturally occurring proteins with 90% identity thereto, or proteins comprising biologically active or immunogenic fragments thereof.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of SEQ ID NO: 1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In this case, the specification provides SEQ ID NO: 1. No naturally occurring variants thereof are described, nor are any biological activities described that would allow determination of whether a given fragment was or was not biologically active. Further, as the claims encompass proteins *comprising* biologically or immunogenically active fragments of SEQ ID NO: 1, which might be embedded in other proteins (see art rejection, below), there is no written description of such

proteins.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 1 or isolated fragments thereof, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As no naturally occurring sequences having 90% identity to SEQ ID NO: 1 are described, the metes and bounds of claim 1 cannot be determined. It cannot be determined which 90% identical sequences are or are not naturally occurring.

Claim 16 is further indefinite as it is not clear for what the excipient is to be acceptable; therefore, the metes and bounds of the claim cannot be determined.

Claims 2 and 17 are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a)

of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Kleyn et al., U.S. Patent Number 5,646,040.

Kleyn et al. teach the mammalian TUB gene. SEQ ID NO: 8 of Kleyn et al. is 49.6% identical to residues 14-439 of SEQ ID NO: 1 of this application, and comprises several regions of identity, including one of 17 residues, at amino acids 308-325 of SEQ ID NO: 1, which meets the limitation of being a protein comprising an immunogenic fragment of SEQ ID NO: 1, and possibly also of comprising a biologically active fragment of SEQ ID NO: 1. Pharmaceutical compositions are disclosed at columns 35-36. Additionally, it is disclosed to use such compositions to make antibodies. Accordingly, the claims are anticipated by the disclosure of Kleyn et al.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703)746-5228.

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner

09/782390.1
9/20/02